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Metal-Catalyzed Carboxylation of Organic (Pseudo)halides with CO_2

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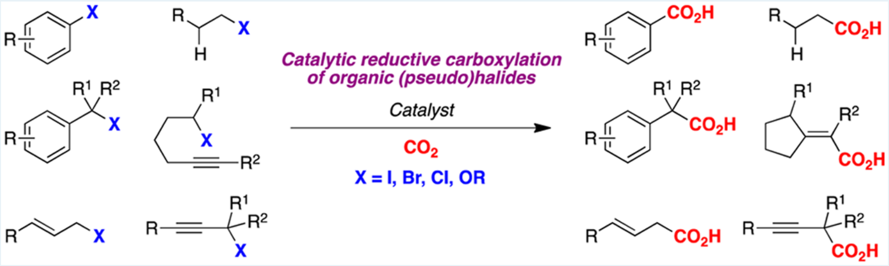

ABSTRACT: The recent years have witnessed the development of metal-catalyzed reductive carboxylation of organic (pseudo)halides with CO_2 as C1 source, representing potential powerful alternatives to existing methodologies for preparing carboxylic acids, privileged motifs in a myriad of pharmaceuticals and molecules displaying significant biological properties. While originally visualized as exotic cross-coupling reactions, a close look into the literature data indicates that these processes have become a fertile ground, allowing for the utilization of a variety of coupling partners, even with particularly challenging substrate combinations. As for other related cross-electrophile scenarios, the vast majority of reductive carboxylation of organic (pseudo)halides are characterized by their simplicity, mild conditions, and a broad functional group compatibility, suggesting that these processes could be implemented in late-stage diversification. This perspective describes the evolution of metal-catalyzed reductive carboxylation of organic (pseudo)halides from its inception in the pioneering stoichiometric work of Osakada to the present. Specific emphasis is devoted to the reactivity of these coupling processes, with substrates ranging from aryl-, vinyl-, benzyl- to unactivated alkyl (pseudo)halides. Despite the impressive advances realized, a comprehensive study detailing the mechanistic intricacies of these processes is still lacking. Some recent empirical evidence reveal an intriguing dichotomy exerted by the substitution pattern on the ligands utilized; still, however, some elementary steps within the catalytic cycle of these reactions remain speculative, in many instances invoking a canonical cross-coupling process. Although tentative, we anticipate that these processes might fall into more than one distinct mechanistic category depending on the substrate utilized, suggesting that investigations aimed at unraveling the mechanistic underpinnings of these processes will likely bring new and innovative research grounds in this vibrant area of expertise.

KEYWORDS: *catalysis, carbon dioxide, nickel, cross-coupling, carboxylic acid*

1. INTRODUCTION

In recent years, the functionalization of carbon dioxide (CO_2) into organic matter has received considerable attention.[1] Such interest arises from the fact that CO_2 is the primary greenhouse gas emitted through human activities due to the industrial development of our society. Although CO_2 fixation in synthetic endeavors will likely not reduce dramatically its concentration in the atmosphere, the low cost, endless availability, and benign character of CO_2 hold promise to revolutionize synthetic approaches for preparing high-value-added chemicals from simple renewable feedstock, thus making a better use of energy and carbon.[2] Despite its thermodynamic stability and kinetic inertness, a number of strategies have been designed for promoting CO_2 fixation, even at industrial scale.[1−3] At present, the vast majority of synthetic applications for CO_2 fixation into organic matter are predominantly based on C−O bond-forming reactions or reduction events en route to methanol, formic acid, or methane.[4] Indeed, it is estimated that approximately 110 megatons of CO_2 are annually being employed in the chemical industry for preparing urea, carbonates or salicylic acid.[2,5] In sharp contrast, however, the ability to promote *catalytic* CO_2 fixation techniques via *C*−*C bond-forming* reactions still remains a relatively unexplored terrain, particularly in industrial settings, hence representing a formidable opportunity to increase our ever-growing chemical arsenal for preparing compounds of utmost synthetic relevance for both academic and pharmaceutical laboratories.

Carboxylic acids rank among the most ubiquitous motifs in a myriad of compounds that display significant biological properties (Scheme 1).[6] Actually, the presence of these frameworks and/or their derivatives in pharmaceuticals is so pervasive that the inclusion of the carboxylic acid function is

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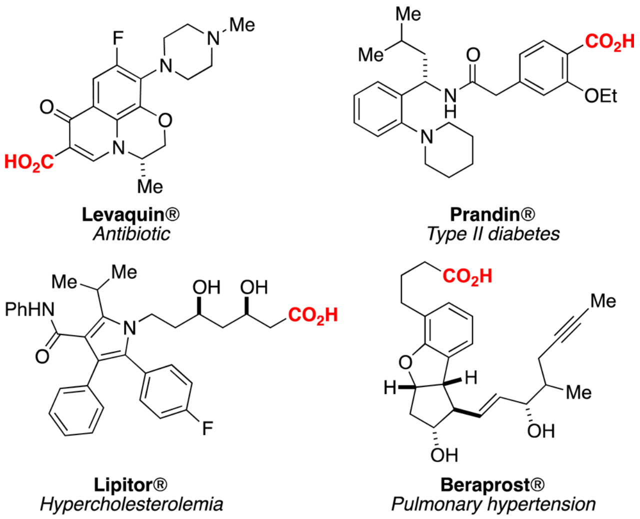
Scheme 1. Biological Relevance of Carboxylic Acids



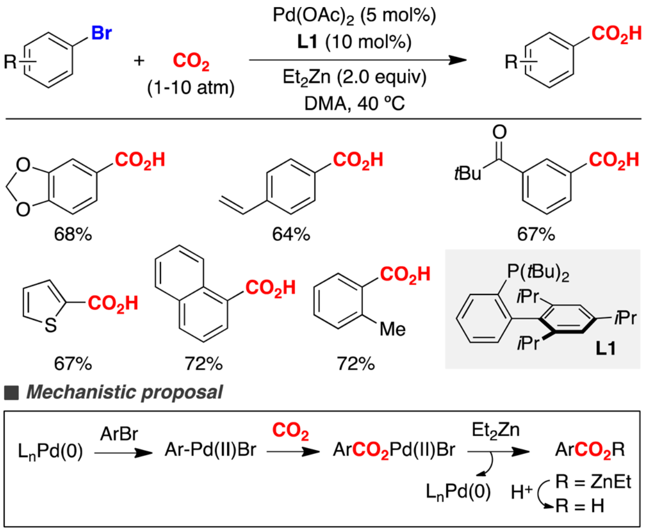
often visualized as a requisite in industrial venues. Although our synthetic portfolio includes a wide variety of robust and reliable synthetic protocols for their synthesis,[7] there is ample consensus that the importance of carboxylic acids and their prevalence in pharmaceuticals requires the design of new *catalytic* carboxylation methodologies with improved practicality, chemoselectivity, and generality. To such end, chemists have been challenged to develop unconventional, yet efficient, catalytic techniques that make use of simple, cheap, and available raw materials for preparing synthetically valuable carboxylic acids. Among the different alternatives, the means to utilize CO_2, the simplest alternative feedstock, is particularly appealing. Prompted by its low thermodynamic potential, it comes as no surprise that initial efforts toward the implementation of carboxylation protocols using CO_2 were conducted using stoichiometric, highly reactive, and in many instances, air-sensitive organometallic species such as organolithium, Grignard reagents, or organozinc derivatives.[8] Although formidable advances have been realized with less-nucleophilic entities,[9] the use of well-defined organometallic reagents might reduce the applicability of these methods, particularly when dealing with late-stage diversification or densely functionalized backbones, thus reinforcing a change in strategy.

Taking into consideration that stoichiometric organometallic species are frequently prepared from organic halides, an ideal scenario within the carboxylation arena would be the use of organic (pseudo)halides as coupling partners, thus avoiding the need for well-defined and stoichiometric organometallic reagents. By definition, the carboxylation of organic (pseudo) halides falls into the category of catalytic cross-electrophile coupling reactions.[10] Unlike classical cross-electrophile reactions based on homogeneous precursors, catalytic carboxylation processes operate with CO_2, a rather unreactive electrophile that is not particularly soluble in regular organic solvents employed in the cross-coupling arena, constituting a formidable challenge from both a conceptual and technological standpoint. As evident from the wealth of literature data reported in recent years, the metal-catalyzed reductive carboxylation of organic (pseudo)halides has reached remarkable levels of sophistication, representing powerful alternatives for preparing carboxylic acids from simple precursors. Interestingly, the vast majority of these processes operate at atmospheric pressure of CO_2, constituting an important bonus when compared with other CO_2 fixation techniques.[1] Outlined below is a detailed overview over this emerging field of expertise, which does not cover neither catalytic carboxylation protocols of unsaturated compounds nor electrocatalytic processes, as these methods have recently been reviewed elsewhere.[11,12] Although significant carboxylation techniques have been reported in the absence of a metal catalyst,[13] the purpose of this Perspective is to summarize the most significant developments in catalytic reductive carboxylation of organic (pseudo)halides with CO_2 as C1 source, including mechanistic discussions and future aspects, when appropriate.

2. DIRECT CATALYTIC CARBOXYLATION OF ORGANIC HALIDES WITH CO_2

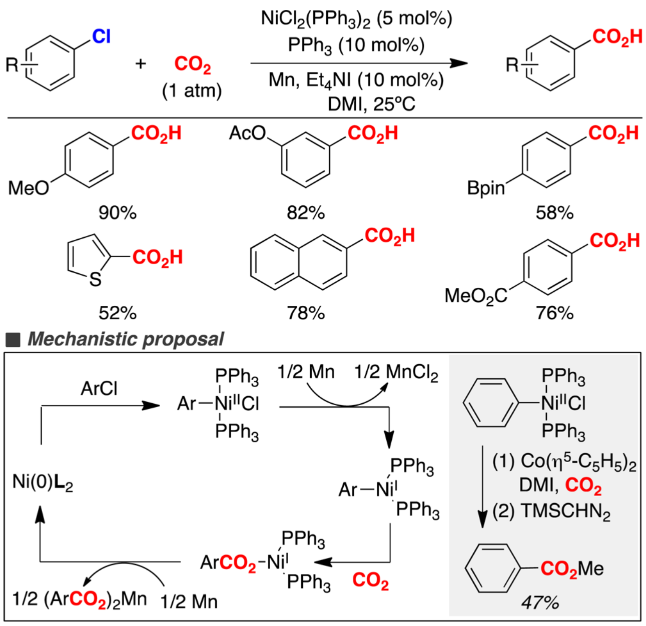
2.1. Catalytic Carboxylation of Aryl Halides. In 1994, pioneering studies by Osakada and Yamamoto showed that well-defined Ph-Ni(L)Br (L = bpy) reacted with CO_2 at atmospheric pressure to afford benzoic acid in moderate yield.[14] Although stoichiometric Ni species were required, this study tacitly demonstrated the feasibility for promoting a CO_2 insertion into the Ar−Ni bond, setting the stage for designing catalytic carboxylation techniques. Surprisingly, this topic remained dormant for some years, and it was only recently that these processes could be implemented in a catalytic fashion. Specifically, our group reported in 2009 a Pd-catalyzed carboxylation of aryl bromides with CO_2 (1−10 atm) using Et_2Zn as reducing agent (Scheme 2).[15] The nature of the ligand turned out to be critical, with particularly bulky and electron-rich *t*BuXPhos providing the best results while minimizing parasitic dehalogenation or Negishi-type reactions. Under these conditions, a wide number of functional groups ranging from amines, ketones, (thio)ethers, or alkenes to even epoxides could be tolerated. Although one might have anticipated the involvement of arylzinc intermediates, control reactions employing either PhZnBr or D_2O quenching experiments suggested otherwise. On the basis of these results, the proposed pathway was a CO_2 insertion into the in situ-generated Ar−Pd(II)Br oxidative addition complex followed by a final transmetalation with Et_2Zn, thus forming a zinc benzoate while regenerating the catalytic competent $L_nPd(0)$ species.

Scheme 2. Pd-Catalyzed Carboxylation of Aryl Bromides



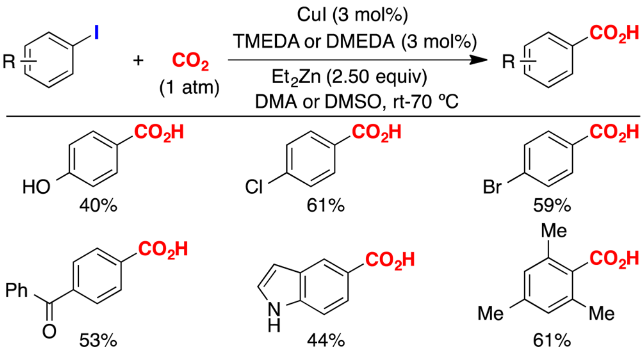
While the carboxylation of aryl bromides (Scheme 2) undoubtedly constituted a proof-of-concept for designing catalytic carboxylation techniques of organic halides,[15] the need for pyrophoric reagents (i.e., Et_2Zn), high pressures (1−10 atm), and the restriction to aryl bromides constituted serious drawbacks to be overcome. To this end, Tsuji and Fujihara described a Ni-catalyzed carboxylation of aryl chlorides using simple Mn as reductant and ammonium salts as additives (Scheme 3).[16] Strikingly, the nature of the latter had a profound influence on reactivity, with Et_4NI being particularly suited for effecting the carboxylation. In contrast with our findings using aryl bromides,[15] the presence of bulky or electron-rich phosphines had a deleterious effect on reactivity; indeed, PPh_3 and bipyridine provided the best results for aryl and vinyl chlorides, respectively. The authors proposed a mechanism that is somewhat reminiscent of electrocatalytic carboxylations in which an aryl−Ni(I) is generated upon single-electron transfer (SET),[17] likely facilitated by Et_4NI,[18] a notion that was corroborated by stoichiometric experiments with $PhNiCl(PPh_3)_2$ and $Co(\eta^5\text{-}C_5H_5)_2$ as well as theoretical calculations.[19] A final CO_2 insertion into the $C(sp^2)−Ni(I)$ bond followed by SET mediated by Mn would regenerate the $L_nNi(0)$ species while forming the targeted carboxylic acid upon final hydrolytic workup.

Scheme 3. Ni-Catalyzed Carboxylation of Aryl Chlorides



In 2013, Daugulis described a Cu/TMEDA regime for the catalytic carboxylation of aryl iodides using Et_2Zn as reducing agent (Scheme 4).[20,21] In line with our results dealing with aryl bromides,[15] the presence of Et_2Zn did not have a deleterious effect, as a number of functional groups could be accommodated perfectly. Even hindered substrate combinations could be within reach at room temperature when using DMEDA as ligand, a significant finding when compared to previous carboxylation techniques. The authors supported a mechanistic scenario similar to that proposed in Scheme 2 with a CO_2 insertion occurring at the in situ-generated $C(sp^2)−Cu$ bond followed by transmetalation with Et_2Zn.

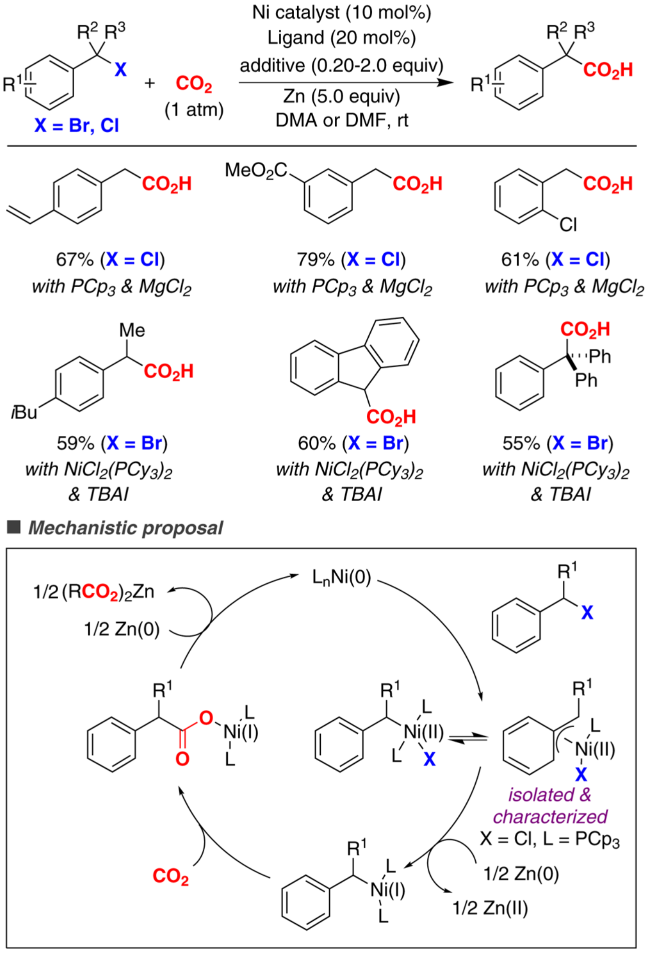
Scheme 4. Cu-Catalyzed Carboxylation of Aryl Iodides



2.2. Catalytic Carboxylation of Benzyl Halides.

Although the synthesis of benzoic acids highlighted in Schemes 2−4 led to the foundation of modern catalytic carboxylation reactions of organic halides, these catalytic endeavors should, by no means, be limited to the coupling of aryl halides. Driven by the prevalence of phenylacetic acids in molecules that display significant biological activities such as vancomycin, carbenicillin, or ibuprofen, among others,[6] our group described a Ni-catalyzed reductive carboxylation of primary, secondary, or even tertiary benzyl halides with CO_2 at atmospheric pressure and Zn dust as reductant (Scheme 5).[22] The role of additives was found to be critical, with $MgCl_2$ and TBAI providing the best results when dealing with the coupling of primary or secondary/tertiary benzyl halides, respectively. Under these

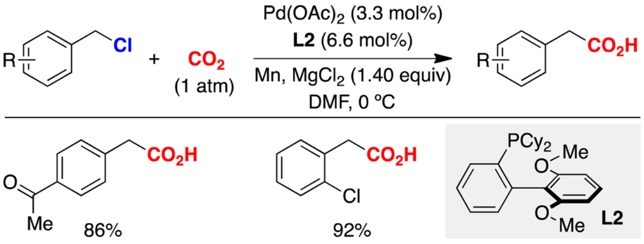
Scheme 5. Ni-Catalyzed Carboxylation of Primary, Secondary, and Tertiary Benzyl Halides



conditions, a variety of functional groups could be accommodated, including alkenes, ketones, esters, or even aryl halides, thus leaving ample room for orthogonal modifications. By definition, the direct carboxylation of benzyl halides represent a synthetic alternative to an otherwise related hydrocarboxylation of styrenes with CO_2;[23] unlike the latter, however, the utilization of primary, secondary, or even tertiary benzyl halides confers an improved flexibility in synthetic design. Preliminary stoichiomeric studies with isolated η^3-benzylnickel(II) species in the absence and presence of external reductant allowed for establishing a mechanistic rationale. Specifically, a pathway was proposed that was somewhat reminiscent of the Cr-catalyzed Nozaki–Hiyama–Kishi reaction,[24] in which an initial oxidative addition produces a η^1/η^3–benzylnickel(II) species that subsequently undergoes SET mediated by Zn.[17] The corresponding benzylnickel(I) species might react with CO_2,[25] delivering a nickel(I) carboxylate that ultimately generates the targeted phenylacetic acid upon SET followed by aqueous workup while regenerating the active $L_nNi(0)$ catalyst. In 2014, a detailed theoretical study using DFT calculations revealed the important role of $MgCl_2$ for either stabilizing a Ni(I)-CO_2 complex prior to CO_2 insertion, or favoring SET-type processes.[26]

More recently, He reported an alternate protocol for effecting the reductive carboxylation of primary benzyl halides using Pd catalysts and Mn as reducing agent (Scheme 6).[27] In line with the corresponding Pd-catalyzed carboxylation of aryl bromides,[15] highly electron-donating and bulky phosphine ligands were found to be critical for minimizing dimerization and dehalogenation pathways. In this case, $MgCl_2$ was proposed to act as Lewis acid for facilitating CO_2 insertion into the benzylic C(sp^3)–Pd(II) bond, thus setting the stage for a final reduction promoted by Mn, delivering a manganese carboxylate with concomitant regeneration of $L_nPd(0)$.

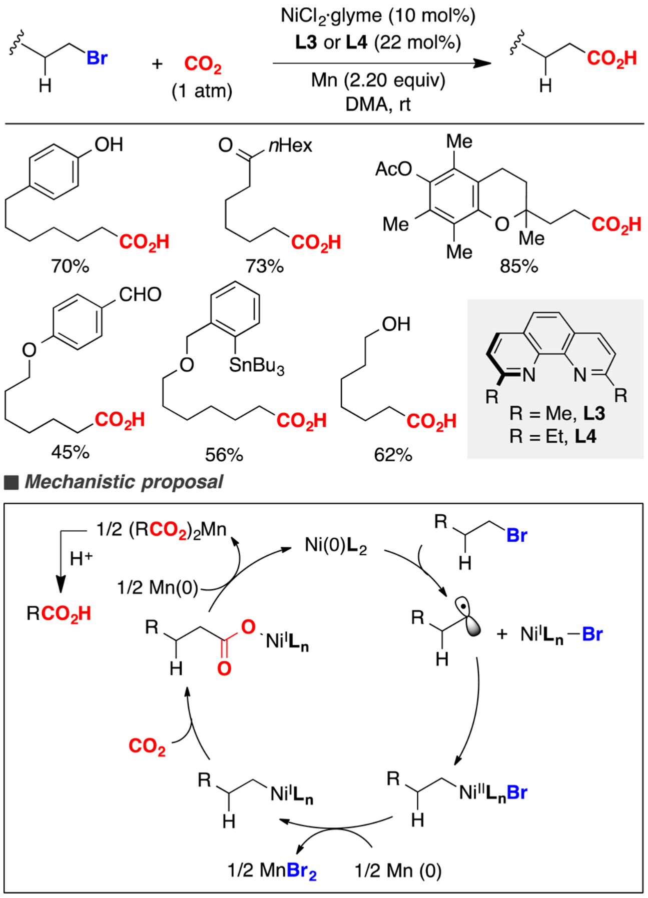
Scheme 6. Pd-Catalyzed Carboxylation of Primary Benzyl Chlorides



2.3. Catalytic Carboxylation of Unactivated Alkyl Halides Possessing β-Hydrogens.

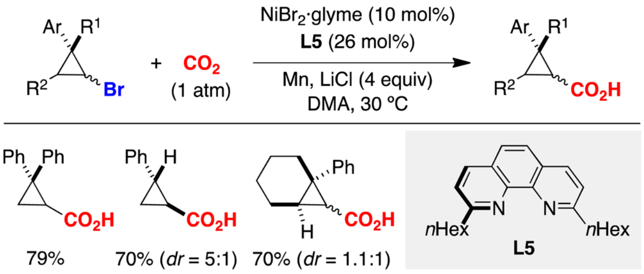
In view of the available literature data reported until late in 2013, it became apparent that the catalytic reductive carboxylation arena seemed to be inherently restricted to substrates that rapidly underwent oxidative addition such as aryl or benzyl halides. Such observation suggested that the extension to unactivated alkyl halides possessing β-hydrogens would be a futile effort given their reluctance to undergo oxidative addition and the proclivity of the in situ-generated alkyl metal species toward destructive β-hydride elimination or homodimerization pathways.[28] Challenged by this perception, our group initiated a program to unravel the potential of catalytic carboxylation techniques of unactivated alkyl halides containing β-hydrogens. Unlike previous carboxylation strategies of aryl or benzyl halides based on phosphine ligands, the best results for the carboxylation of unactivated alkyl bromides were achieved when utilizing Ni precatalysts with bidentate nitrogen-containing ligands, particularly 1,10-phenanthroline backbones (Scheme 7).[29] Although certainly not anticipated, it was found that the inclusion of *ortho*-substituents adjacent to the nitrogen atom was critical for success. It was speculated that an increased steric bulk around the nitrogen donor ligand could result in greater stability of intermediate Ni(II) or the in situ-generated Ni(I) complexes upon SET-processes. Under a Ni/**L3** or Ni/**L4** regime, an excellent functional group compatibility was observed, as nitriles, ketones, aldehydes, unprotected alcohols, aryl halides, or even aryltin motifs, among others, could be perfectly accommodated. These findings constituted a bonus when compared with the classical carboxylation of air-sensitive, stoichiometric, and rather reactive alkyl organometallic species with CO_2.[8] Importantly, the formation of a statistical mixture of carboxylic acids from diastereomerically pure α,β-bisdeuterated alkyl bromides supported the notion that SET-type processes might be operative, pointing toward the involvement of Ni(I) intermediates.

Scheme 7. Ni-Catalyzed Direct Carboxylation of Unactivated Alkyl Bromides



In early 2016, the means to promote catalytic reductive carboxylation of secondary organic halides remained confined to substrates possessing adjacent π-components such as aromatic rings,[22] probably due to the stabilization of the putative reaction intermediates. Recently, our group partially addressed this limitation by designing a Ni-catalyzed reductive carboxylation of bromocyclopropane derivatives (Scheme 8).[30] The rationale behind the observed reactivity was attributed to

Scheme 8. Ni-Catalyzed Reductive Carboxylation of Cyclopropyl Bromides

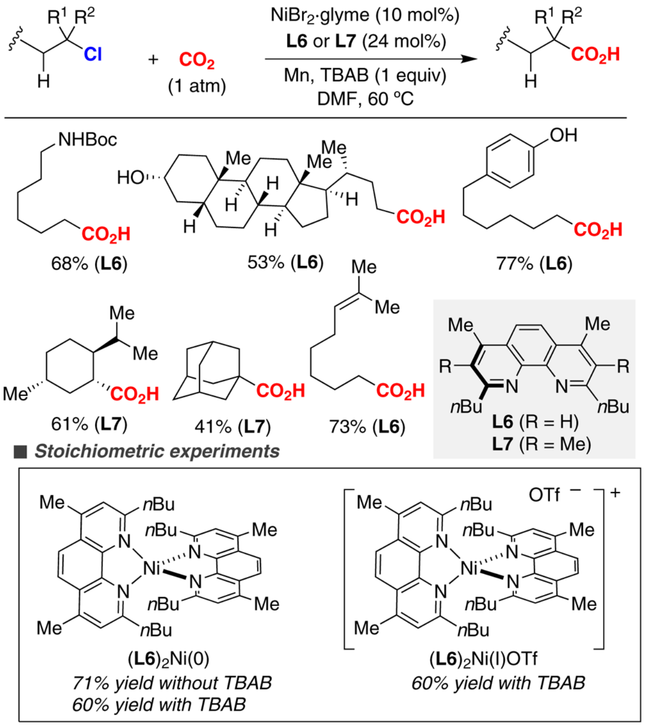


the ring strain and orbital rehybridization of cyclopropyl rings,[31] thus facilitating the targeted carboxylation event. In line with the carboxylation of unactivated alkyl bromides (Scheme 7),[29] it was found that the combination of *ortho*-substituted 1,10-phenanthrolines such as **L5** with LiCl provided the best results while avoiding competitive ring-opened products. Interestingly, *cis*/*trans* ratios were invariably observed for unsymmetrically substituted substrates, regardless of whether diastereomerically pure *trans*- or *cis*-cyclopropyl bromides were utilized, thus suggesting the intermediacy of SET-processes via Ni(I) reaction intermediates.[17] It is worth noting, however, that a single diastereoisomer was found when promoting an otherwise similar carboxylation but employing cyclopropene derivatives, thus showing that modifications on the substrate might lead to different reaction mechanisms. Interestingly, stoichiometric studies with (**L3**)$_2$Ni(0) species revealed that the reaction required the utilization of Mn, thus reinforcing the notion that SET-type processes intervene in these reactions.

Despite the advances realized, the direct carboxylation of unactivated secondary or tertiary organic halides still constituted a chimera; additionally, no examples of unactivated alkyl chlorides were reported. To such end, our group recently reported a catalytic carboxylation of unactivated primary, secondary, and even tertiary alkyl chlorides that occurred with an exquisite chemoselectivity profile at atmospheric pressure of CO$_2$ (Scheme 9).[32] Notably, this protocol demonstrated that *intermolecular* cross-electrophile coupling of unactivated alkyl chlorides could be within reach, thus exploiting a previously unrecognized opportunity in this field.[10] As for previous catalytic carboxylation techniques,[29,31] the presence of *ortho*-substituents on the phenanthroline backbone and the role of additives were found to be critical, with a combination of **L6**/**L7** and *n*Bu$_4$NBr (TBAB) showing the best results.[18]

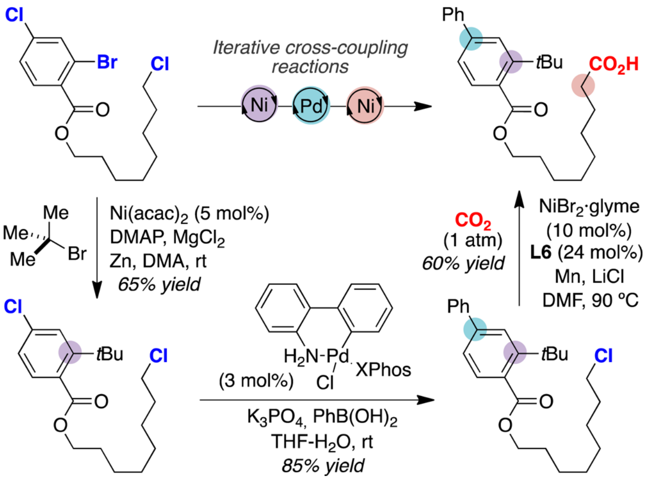
Although one might argue that a Br/Cl exchange could occur in the presence of TBAB, control experiments revealed otherwise; indeed, similar reactivity was found when using LiCl instead of TBAB. As for the carboxylation of unactivated primary alkyl bromides,[29] stereochemical studies by isotope-labeling suggested the involvement of radical intermediates via SET-type processes. As expected, both (**L6**)$_2$Ni(0) and (**L6**)$_2$Ni(I) (OTf) were found to be competent as reaction intermediates when using 1-(4-chlorobutyl)-4-methoxybenzene as substrate, and high yields of the corresponding carboxylic acid were obtained regardless of whether these complexes were used in a catalytic or stoichiometric fashion. Importantly, it was found that the carboxylation occurred even *in the absence* of TBAB, thus reinforcing the notion that a Cl/Br exchange is not required. These results suggested that the reaction is initiated by the formation of discrete alkyl-Ni(II)Cl species generated upon a nonclassical oxidative addition based on a SET followed by recombination with the corresponding Ni(I)Cl.

Scheme 9. Ni-Catalyzed Carboxylation of Unactivated Primary, Secondary, or Tertiary Alkyl Chlorides



The success of this reaction suggested that this technique could be adapted in iterative cross-coupling scenarios of polyhalogenated backbones.[33] As shown in Scheme 10, this turned out to be the case. Specifically, it was found that a cross-electrophile protocol reported by Gong[34] with *tert*-butyl bromide resulted in the exclusive formation of the targeted product bearing an all-carbon quaternary center in 65% yield. Suzuki−Miyaura cross-coupling reaction based on the employment of one-component Pd(II)-precatalysts popularized by Buchwald[35] with PhB(OH)$_2$ took place exclusively at the aryl chloride motif. A final exposure under a Ni/**L6** regime easily

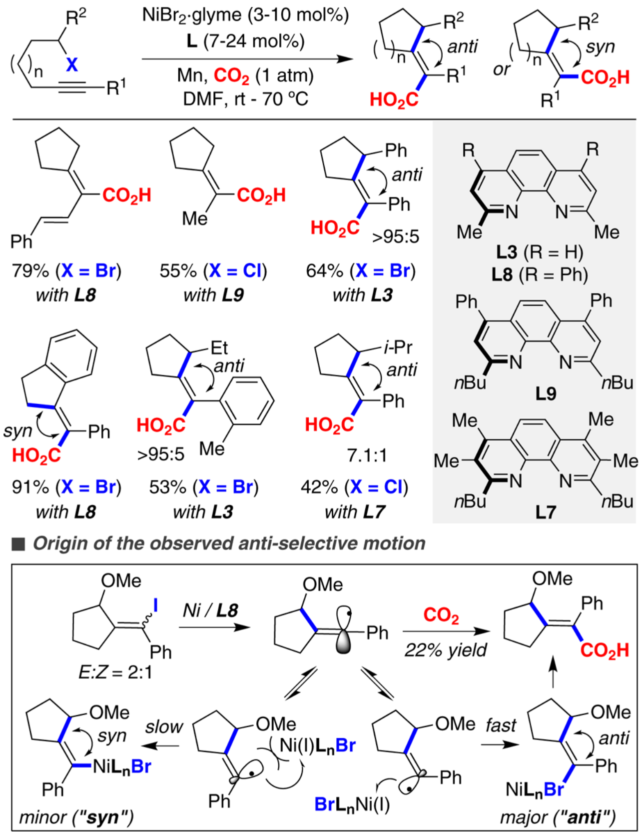
Scheme 10. Iterative Cross-Coupling Reactions of Polyhalogenated Backbones



promoted the carboxylation of the unactivated alkyl chloride residue, affording the targeted alkyl carboxylic acid in 60% yield.

At first sight, the involvement of SET-processes in catalytic carboxylation of unactivated alkyl halides might be visualized as an important drawback to be overcome, as enantioenriched precursors ultimately ended up in racemic materials. However, such observation could be turned into a strategic advantage for promoting cascade carboxylation reactions initiated by SET-type processes, thus setting the basis for biomimetic carboxylation events. Specifically, our research group found that alkyl halides possessing alkyne motifs at an appropriate position within an alkyl side-chain could trigger a tandem cyclization/carboxylation reaction en route to five- or even six-membered rings, thus giving access to rather elusive tetrasubstituted carboxylated olefins in which CO_2 insertion takes place at a distal reaction site (Scheme 11).[32,36] The optimization of the reaction conditions evidenced a delicate interplay between all the reaction components; although a cocktail based on **L3** or **L8** was suitable for alkyl bromides,[36] **L7** and **L9** showed to be superior for alkyl chlorides.[32] More importantly, this technology was distinguished by an intriguing divergence in *syn*/*anti*-selectivity that could be easily dictated by the ligand or substrate utilized when operating with secondary alkyl halides. Isotope-labeling studies and stoichiometric experiments with $L_2Ni(0)$ species suggested that while primary alkyl halides follow a classical oxidative addition pathway, the origin of the *anti*-selective motion found in secondary alkyl halides might be interpreted via SET-type processes. The rationale behind such observation is tentatively ascribed to the intermediacy of two vinyl radicals with sp^2-character that can rapidly interconvert prior recombination with the corresponding LNi(I)X species. The observed *anti*-motion can be attributed to a preferential recombination of the vinyl radical with the Ni center by avoiding the clash with the substituents originally located at the alkyl halide terminus. Indirect evidence for such a pathway was obtained when observing a single carboxylic acid with an *anti*-motion upon exposure of iodo(2-methoxycyclopentylidene)methylbenzene (*E*:*Z* = 2:1) under the optimized reaction conditions (Scheme 11, bottom).

Scheme 11. Ni-Catalyzed Cyclization/Carboxylation of Unactivated Alkyl Halides



It is evident that the catalytic reductive carboxylation of organic halides has reached remarkable levels of sophistication, allowing for the coupling of aryl,[15,16,20] benzyl,[22,27] or even the always-challenging unactivated alkyl halides possessing *β*-hydrogens,[29,32,36] thus demonstrating the versatility, potential, and the application profile of these methodologies.[13] At first sight, one might argue that this field of expertise has reached its full potential; however, the lack of enantioselective or stereospecific reductive carboxylation reactions of organic halides to prepare enantioenriched carboxylic acids indicates otherwise. Taking into consideration the recent developments in catalytic enantioselective transformations, it is inevitable to predict a bright future within the area of catalytic asymmetric carboxylation.

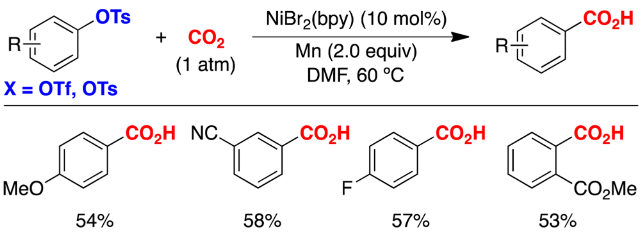
3. DIRECT CATALYTIC CARBOXYLATION OF C–HETEROATOM BONDS WITH CO_2

3.1. Catalytic Carboxylation of Organic Sulfonates via C–O Cleavage.

The success of cross-coupling reactions of organic halides contributed to the perception that these reactions could only be executed efficiently if an organic halide is utilized as coupling partner.[37] However, the toxicity associated with the halogenated waste and the difficulties for accessing organic halides in advanced synthetic intermediates still constituted serious drawbacks to be overcome. Not surprisingly, the search for alternative coupling partners has recently been taken up with considerable rigor. Among these, C–O electrophiles have recently emerged as powerful alternatives to organic halides in cross-coupling reactions due to their low toxicity, ready availability, and natural abundance of alcohols.[38] The first example of a catalytic CO_2 insertion into C–O bonds was reported by Tsuji and Fujihara using aryl tosylates and triflates under similar conditions to those employed for the carboxylation of aryl chlorides with a regime based on $NiCl_2(PPh_3)_2$ and Et_4NI as additive (Scheme 3).[16] Recently, Durandetti extended the scope of these reactions by using $NiBr_2(bpy)$ as precatalyst in the absence of halogenated additives (Scheme 12).[39] Although moderate yields were obtained under these reaction conditions, a wide variety of electron-rich or electron-poor aryl tosylates could be employed, including *ortho*-substituted precursors.

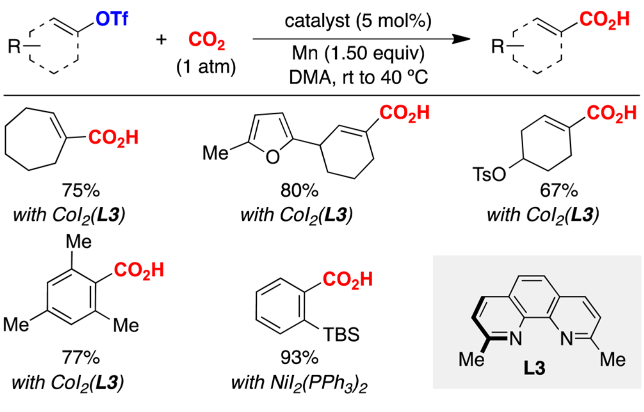
While Tsuji and Fujihara demonstrated the ability of Ni catalysts to efficiently promote the carboxylation of aryl and

Scheme 12. Ni-Catalyzed Carboxylation of Aryl Tosylates



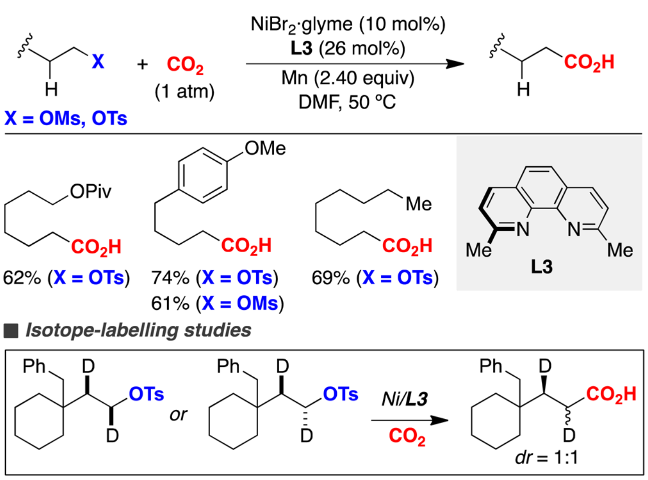
vinyl chlorides (Scheme 3),[16] the carboxylation of particularly hindered substrate combinations was still rather problematic. Taking these observations into consideration, in 2015 Tsuji and Fujihara described the catalytic carboxylation of alkenyl as well as sterically encumbered aryl triflates utilizing either Co(II) or Ni(II) precatalysts (Scheme 13).[40] Although the Co-catalyzed carboxylation of alkenyl triflates displayed an excellent chemoselectivity profile, the method remained unfortunately restricted to trisubstituted alkenyl triflates. Still, however, it was found that either CoI_2(**L3**) or $NiI_2(PPh_3)_2$ performed perfectly well for aryl triflates, even for particularly hindered substrate combinations. These results go in line with previous observations made by our group in which the presence of substituents adjacent to the nitrogen atom in 1,10-phenanthroline-type ligands ultimately result in Ni intermediates with superior reactivity and stability.[29,32,36]

Scheme 13. Co- and Ni-Catalyzed Carboxylation of Aryl and Alkenyl Triflates



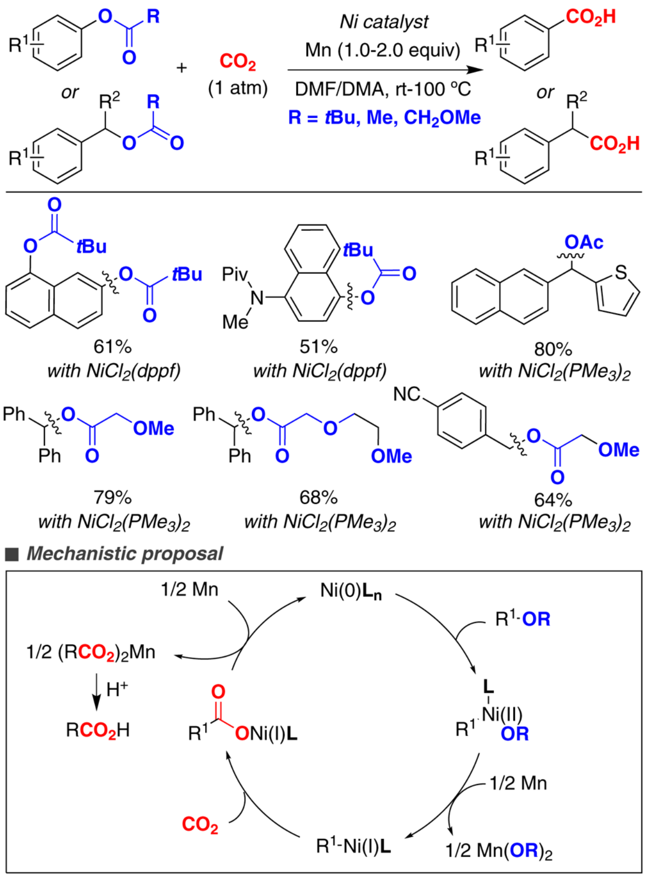
As part of our study on the Ni-catalyzed carboxylation of unactivated alkyl bromides possessing β-hydrogens (Scheme 7),[29] our group found that a catalytic couple based on **L3** and Mn as reducing agent was particularly suited for the carboxylation of unactivated primary alkyl mesylates or tosylates (Scheme 14).[29] The reaction mechanism was believed to follow an otherwise identical rationale to that proposed for primary alkyl bromides based on SET-type processes. In line with this notion, isotope-labeling studies revealed the loss of chemical integrity at C1 when promoting the reaction with diastereomerically pure alkyl tosylates possessing deuterium labels at C1 and C2.

Scheme 14. Ni-Catalyzed Carboxylation of Unactivated Alkyl Sulfonates



3.2. Catalytic Carboxylation of Ester Derivatives via C−O Cleavage. Unlike the utilization of particularly activated organic sulfonates, a limited number of cross-coupling methodologies have been conducted with simpler aryl esters due to the higher energy required for effecting $C(sp^2)-O$ cleavage, the propensity for hydrolysis via C(acyl)−O bond, and site-selectivity issues in the presence of multiple C−O bonds.[38] To this end, our group described the carboxylation of either aryl or benzyl ester derivatives (Scheme 15).[41] As expected, the ligand played a crucial role, with dppf providing the best results when using aryl pivalates as substrates. The superior reactivity of bulky ester derivatives was tentatively attributed to a higher stabilization of the putative reaction intermediates. The extension to benzyl esters was not particularly problematic and either bulky pivalates or regular acetate derivatives could be employed with equal ease with PMe_3 as ligand. Unfortunately, the reaction of both aryl and benzyl esters remained restricted to extended π-systems, a recurrent limitation encountered in a myriad of C−O bond-cleavage scenarios.[42] This limitation could partially be tackled by the use of hemilabile directing groups on the ester motif,[43] thus accelerating the rate of oxidative addition while opening up coordination sites on the Ni center, ultimately facilitating the corresponding CO_2 insertion into the targeted C−O bond. According to previous studies on Ni-catalyzed reductive

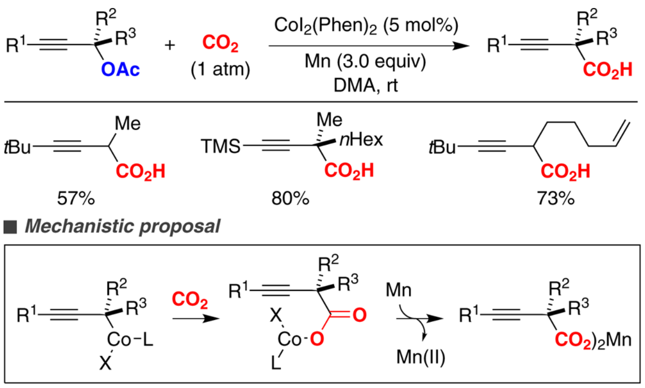
Scheme 15. Ni-Catalyzed Carboxylation of Aryl and Benzyl Ester Derivatives



carboxylations, a catalytic cycle involving SET-processes mediated by Mn to generate Ni(I) species prior CO_2 insertion into the C−Ni bond was proposed.[17,25]

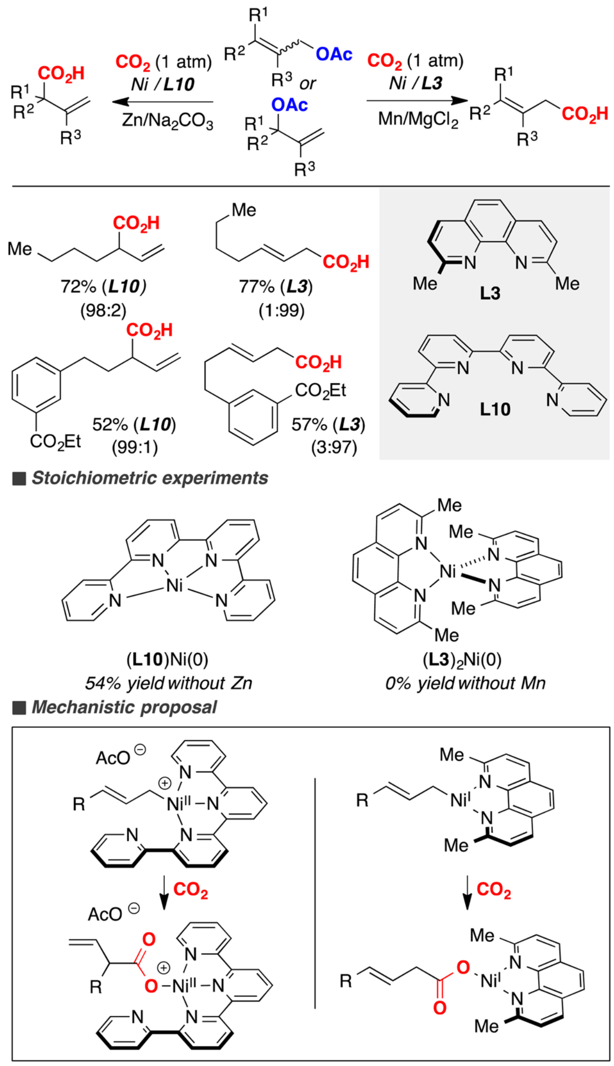
In 2014, Tsuji and Fujihara explored the viability of promoting the catalytic carboxylation of propargyl acetates (Scheme 16).[44] Interestingly, it was found that a catalytic reaction based on CoI_2 was not particularly ligand-dependent; still, however, the best results were accomplished with 1,10-phenanthroline as ligand. While one might expect the participation of allenyl metal intermediates resulting in both propargylic and/or allenyl carboxylic acids, exclusive formation of the former was observed in all cases analyzed.[13] Unfortunately, the reaction was predominantly conducted with secondary or tertiary propargyl acetates and the presence of bulky groups on the alkyne terminus. Although a mechanism consisting of oxidative addition of the propargyl ester to Co(I) was proposed, the participation of allenyl cobalt intermediates cannot be ruled out.

Scheme 16. Co-Catalyzed Reductive Carboxylation of Propargyl Acetates



Catalyst-controlled selectivity in which a common precursor is transformed into two or more different products has recently been the subject of intensive investigations.[45] In late 2014, however, regiodivergent reactions remained restricted to nucleophile/electrophile regimes. To this end, our group questioned whether a regiodivergent reductive carboxylation technique could be implemented by using allyl acetates as substrates, arguing that the ligand backbone could discriminate both ends of the initially formed π-allyl metal complex. This hypothesis turned out to be correct, resulting in a modular technique capable of introducing selectively the carboxylic acid function at either site of the allyl terminus (Scheme 17).[46] Importantly, the reaction was not substrate-controlled, as the ligand backbone exclusively dictated the selectivity pattern regardless of whether linear or α-branched allyl acetates were utilized. Specifically, a protocol based on **L3** resulted in linear carboxylic acids, whereas a selectivity switch was observed when operating with **L10**, obtaining α-branched carboxylic acids. Although the selectivity profile exclusively depended on the ligand utilized, it was found that the role of additives and reducing agent exerted a non-negligible influence on reactivity, with a protocol based on Mn/$MgCl_2$ or Zn/Na_2CO_3 providing the best results for linear and α-branched carboxylic acids, respectively. Notably, it was possible to isolate the putative Ni(0)$(\mathbf{L3})_2$ and Ni(0)(**L10**) species and study their reactivity with CO_2. Unlike the classical tetrahedral environment found for d^{10} complexes in Ni(0)$(\mathbf{L3})_2$, it came as surprise that a square-planar geometry was observed for Ni(0)(**L10**), an observation that probably indicates that the latter should be better described as a Ni(II)(**L10**) complex with a reduced quaterpyridine dianion. Interestingly, while the reducing agent was required when using Ni(0)$(\mathbf{L3})_2$ in a stoichiometric manner, its absence was inconsequential for reactions based on Ni(0)(**L10**). The intermediacy of an allyl-Ni(I)(**L3**) species might account for these results, whereas the observed reactivity for Ni(0)(**L10**) suggests that CO_2 insertion does not take place neither at the C−Ni center nor via allyl-Ni(I) intermediates, but rather at the γ-position. This observation is somewhat reminiscent of the Pd-carboxylation of allenes mediated by multidentate ligands reported by both Iwasawa and Hazari.[47]

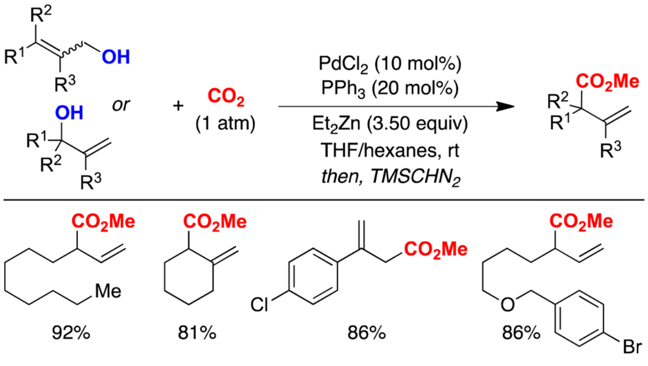
Scheme 17. Ni-Catalyzed Regiodivergent Carboxylation of Allyl Acetates



3.3. Catalytic Carboxylation of Allylic Alcohols.

Recently, the group of Mita and Sato described the Pd-catalyzed carboxylation of allylic alcohols via formal activation of C−OH bonds using Et_2Zn as reducing agent (Scheme 18).[48] In all cases analyzed, α-branched carboxylic acids were exclusively obtained regardless of whether linear or α-branched allyl alcohols were utilized. The authors demonstrated the utility of this protocol by promoting a one-pot carboxylation using simple aldehydes as starting precursors. The observed reactivity was attributed to the coordination of the alcohol

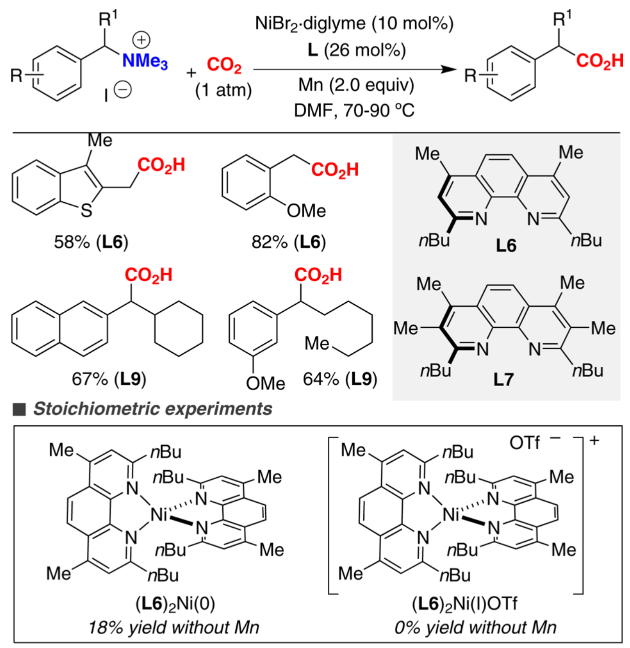
Scheme 18. Pd-Catalyzed Carboxylation of Allyl Alcohols



motif to the Lewis-acidic Zn(II) center, substantially increasing the leaving group capabilities of the alcohol motif. Although the products can be obtained in excellent yields without the need for derivatizing the corresponding allylic alcohols, the method required the utilization of well-defined and air-sensitive organometallic reagents.

3.4. Catalytic Carboxylation of Benzylic Ammonium Salts. Despite the considerable progress in ligand design in the carboxylation arena, the reductive carboxylation of benzylic systems is not as commonly practiced as one might anticipate. Indeed, the available carboxylation portfolio of benzyl electrophiles invariably results in considerable amounts of homodimerization and β-hydride elimination.[22,27] Additionally, these methods are restricted by a rather limited set of substitution patterns. For example, the preparation of phenyl acetic acids possessing α-alkyl residues other than methyl groups still remained elusive. Prompted by these observations, our group recently designed a catalytic carboxylation of air-, thermally stable and highly crystalline ammonium salts via C(sp^3)−N cleavage (Scheme 19).[49] Specifically, it was found that a Ni/**L6** or Ni/**L7** couple outperforms previous carboxylation of benzyl electrophiles,[22,27] resulting in high yields of phenyl acetic acids while avoiding homodimerization and β-hydride elimination. The extension to secondary benzyl ammonium salts possessing β-alkyl chains other than methyl groups and without the requisite for π-extended systems is particularly appealing, giving access to carboxylic acids that would be beyond reach using other carboxylation techniques.

Scheme 19. Ni-Catalyzed Carboxylation of Benzylic Ammonium Salts



As for other carboxylation processes based on 2,2′-substituted phenanthroline ligands,[29,32,36,46] it was possible to isolate and characterize by X-ray crystallography the corresponding Ni(0)(**L6**)$_2$ complex or even the Ni(I)(**L6**)OTf species. As expected, these complexes were found to be catalytically competent as reaction intermediates. Interestingly, a considerable erosion in yield was found when exposing stoichiometric amounts of Ni(0)(**L6**)$_2$ to a model substrate under CO$_2$ atmosphere in the absence of Mn. Although speculative, a mechanistic scenario based on the intermediacy of SET-processes or comproportionation events via the in situ generation of benzyl Ni(I) intermediates was proposed.[50]

In light of the results shown above, it is evident that the utilization of electrophiles other than organic halides has shown to be a viable, yet powerful, alternative to commonly practiced catalytic reductive carboxylation reactions. Still, this field has not reached its full potential, as the utilization of unactivated alcohols or alkyl ethers, elusive counterparts in the cross-coupling arena, still remains unexplored. Additionally, the only successful protocol based on C−N cleavage employs benzyl ammonium salts; certainly, the ability to include unactivated amines, amides or sulfonamides would be highly appreciated, providing new vistas in this area of expertise.

4. SUMMARY AND OUTLOOK

Prompted by the kinetic inertness and the thermodynamic stability of CO$_2$, the means to promote carboxylation reactions was originally thought to be limited to the utilization of stoichiometric, well-defined, and highly reactive organometallic reagents. Seminal studies reported by Osakada in 1994 using *stoichiometric* amounts of transition metal complexes demonstrated that benzoic acids could be within reach from the corresponding aryl halide via CO$_2$ insertion into in situ-generated C(sp^2)−Ni bonds. Intriguingly, this important finding remained dormant for some years, and it was not until 2009 that our group demonstrated that a *catalytic* reductive carboxylation of aryl halides could be within reach if selecting appropriately the supporting ligand and reducing agent. As judged by the wealth of literature data reported in recent years, it is evident that Osakada's discovery, although devoid of any practical application, set the basis for modern catalytic carboxylation of organic (pseudo)halides. The significant growth experienced in this arena has recently allowed to substantially expand the scope of electrophilic partners that can participate in carboxylation processes, including the always-elusive unactivated alkyl halides possessing β-hydrogens. Although one might argue that this field has reached its full potential, this cannot be further from the truth. Indeed, unactivated alkyl alcohols, amines, or ethers, arguably attractive counterparts due to their lower cost, lack of toxicity and wider availability, have yet not been employed in this arena. A remaining issue in these endeavors is the use of super-stoichiometric amounts of reducing agents. In this regard, more environmentally benign reducing agents or the implementation of photocatalytic techniques would be, conceptually and practicality aside, a considerable step forward. Additionally, the current carboxylation portfolio is unfortunately plagued by the employment of high catalyst loadings, an argument that might hinder the implementation of these techniques at industrial settings. Obviously, the means to promote a catalytic C−H carboxylation while avoiding prefunctionalization at the initial reaction site would be an ideal alternative; although some progress has been described in this regard, at present these methodologies remain essentially confined to relatively acidic C−H bonds[51] and the utilization of directing-group methodologies.[52] Additionally, the means to promote enantioselective catalytic reductive carboxylation of organic matter is virtually absent in the literature. Taken together, these observations suggest that there is ample room for implementing greener and more practical catalytic carboxylation reactions.

Despite the recent advances realized, our knowledge on the reaction mechanisms is still in its infancy. Unfortunately, the mechanistic underpinnings of catalytic carboxylation reactions of organic (pseudo)halides remain largely speculative, particularly in Ni-catalyzed processes. This is largely due to the formation of short-lived entities, the presence of low-coordinate species, the exceptional air-sensitivity of the putative reaction intermediates, and the rather enigmatic role of the additives utilized in these endeavors. Although some important empirical observations have been made with the isolation of well-defined $Ni(0)L_n$ species, as well as the discovery that seemingly trivial modifications in the ligand environment dramatically change the reaction outcome, a reliable access to the key reaction intermediates within the catalytic cycle still remains, at present, a chimera. Additionally, preliminary experimental evidence suggest that the catalytic carboxylation of electrophilic partners might fall into more than one distinct mechanistic category, with paramagnetic intermediates likely coming into play. Beyond any reasonable doubt, an in depth study of the kinetic profile of these reactions would certainly shed light onto the reaction mechanism; unfortunately, however, the heterogeneous nature of these processes, with reagents in either gas, liquid, or solid phase makes this task particularly problematic. In view of the serious existing barriers for studying reaction mechanisms in carboxylation processes, one might argue that unraveling the intricacies of these reactions might be a futile effort. We are absolutely confident, however, that efforts toward this goal are of vital importance and that fundamental knowledge will likely arise from understanding how these reactions operate at a molecular level, thus setting the basis for the discovery of conceptually new processes that will definitely drive research in this arena in the years to come.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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